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Resection Margin for Squamous Cell Carcinoma of the Esophagus

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Objective
The safe resection margin in esophagectomy for esophageal squamous cell carcinoma (SCC) was determined based on the extent of epithelial and subepithelial accessory lesions from the main lesions of esophageal SCC.

Background
There have been many reports on the high incidence of a positive resection margin for esophageal cancer. Although there were some studies on the relationships of the proximal clearance to postoperative local recurrence, no pathologic study on the resection margin has been reported.

Methods
Four hundred twenty specimens of a whole resected esophagus were examined histopathologically and the longitudinal length from the main lesion to the five types of accessory lesions was measured on microscopic slides.

Results
Contiguous intraepithelial carcinoma existed in 69 (46%) of 150 sites of main lesions restricted to the mucosa or submucosa and subepithelial lesions existed in 131 (54%) of 245 sites and 82 (55%) of 150 sites of main lesions invading an adventitia and into neighboring structures, respectively. The risk of a positive resection margin due to subepithelial lesions was below 5% at 10 mm in the main lesion, restricted to the submucosa or the muscularis propria, and at 30 mm in the main lesion, invading the adventitia in the potentially curative operation cases.

Conclusion
These clearances of the resection margin, in which the risk of a positive resection margin is below 5%, are acceptable, although these clearances should only be accepted after the extent of epithelial accessory lesions is accurately determined by the Lugol's stain method.

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The complete removal of cancer tissue is one of the most important factors in the successful treatment of patients undergoing surgery for esophageal cancer.[1] The curability in surgery for esophageal cancer—as for colon cancer or gastric cancer—is achieved by both a complete

removal of the cancer tissue in the primary organ and lymph node dissection. It recently was reported that a radical lymph node dissection had improved the prognosis of esophageal cancer.[2] On the other hand, the fact that there have been many reports on the high incidence of a positive resection margin[3–6] still is a major concern in surgery for esophageal cancer.[7]

Although it is better for curability if longer clearance of the resection margin is indicated, an esophagectomy for cancer of the upper esophagus with a long resection margin occasionally requires a laryngectomy with a permanent tracheostomy. In view of the development of postoperative complications and the postoperative food passage, an intrathoracic reconstruction after a distal partial esophagectomy was shown to be superior to reconstruction after the resection of the whole thoracic esophagus.[8,9] However, the priority of curability in surgery for cancer has posed a dilemma to surgeons because there have been few reports on the safe resection margin in esophagectomy for esophageal cancer.

Many studies of a distal resection margin for rectal cancer have been done to help choose between a lower anterior resection or abdominoperitoneal resection.[10–14] The safe surgical margin for rectal cancer has been explored in two ways—first, by a clinical follow-up study on the relationships of the distal clearance to postoperative local recurrence,[10,11] and second, by a pathologic examination of resected specimens.[12–14] Although there have been some studies on local recurrence after esophagectomy for esophageal cancer,[4,5] no pathologic examination with close attention to the resection margin has been reported yet. In the current study, we made step-sectioned specimens of the whole resected esophagus and histopathologically examined them while paying close attention to five types of accessory lesions that existed beyond the proximal and distal border of the main lesion. The five types of accessory lesions consisted of two epithelial lesions and three subepithelial lesions; the former were intraepithelial carcinoma contiguous to the main lesion and intraepithelial carcinoma existing separately from the main lesion, whereas the latter included subepithelial direct extension, intramural metastasis, and either lymphatic or blood vessel invasion.

MATERIALS AND METHODS

The esophagi of 420 patients who underwent esophagectomies from 1980 to 1993 at the Department of Surgery II, Kyushu University Hospital, and affiliated hospitals were investigated. The ages of patients ranged from 38 to 83 years. Three hundred sixty-nine were men and 51 were women. Histologically, all lesions were squamous cell carcinoma (SCC)—i.e., any histologic types other than SCC were excluded from this study. The 420 specimens consisted of 16 total esophagectomies, 4 cervical esophagectomies, 321 subtotal esophagectomies, 76 distal partial esophagectomies, and 3 transhiatal esophagectomies. Two hundred eighty patients were resected after preoperative treatment including radiotherapy, chemotherapy, and hyperthermia,[15,16] whereas 140 patients were resected without any preoperative treatment.

The specimens were received fresh, opened longitudinally, and pinned onto a cork board. After fixation in 10% formalin, longitudinal step-sectioned blocks, each measuring 0.5 cm in thickness, were made of the whole resected esophagus. After each section was stained with hematoxylin and eosin and examined for the depth and spread of the main lesion and for the presence or absence of accessory lesions, a histologic mapping diagram was made for each specimen. Next, the longitudinal length from the border of the main lesion to the opposite border of the accessory lesion was measured on microscopic slides (Fig. 1A). The measurement was done both at the proximal and distal sites of the main lesion in each specimen. In cases in which more than two main lesions existed, the measurement was done on the proximal site of the proximal main lesion and on the distal site of the distal main lesion (Fig. 1B). The border of the main lesion was defined as the site where the basement membrane of the epithelium was destroyed.

Regarding epithelial accessory lesions, intraepithelial carcinoma contiguous to the main lesion (contiguous IEC; Fig. 2A) and intraepithelial carcinoma existing separately from the main lesion (isolated IEC; Fig. 2B) were investigated. For the diagnosis of intraepithelial carcinoma, we followed the criteria of Suckow et al. for intraepithelial carcinoma.[17] These included the following: 1) the absence of cellular differentiation with variations in size or shape and the hyperchromatism of the nuclei with increased mitotic activity; 2) the aforementioned changes that involved the entire thickness of the epithelium and possibly involved submucous glands and ducts; 3) an intact basement membrane.

Regarding subepithelial accessory lesions, we investigated subepithelial direct extension (Fig. 2C), intramural metastasis (Fig. 2D), and lymphatic or blood vessel invasion (Fig. 2E). Because the subepithelial accessory lesions often coexisted, a length of the subepithelial lesion that existed at the most distant site from the main lesion was measured. A subepithelial direct extension was a part of the main lesion, which progressed to continuity under the epithelium, whereas intramural metastasis and lymphatic or blood vessel invasion existed apart from the proximal or distal border of the main lesion. For the diagnosis of intramural metastasis, we followed the criteria of Takubo et al.[18] These included the following: 1) a metastatic tumor in the esophagus or stomach from the pri-

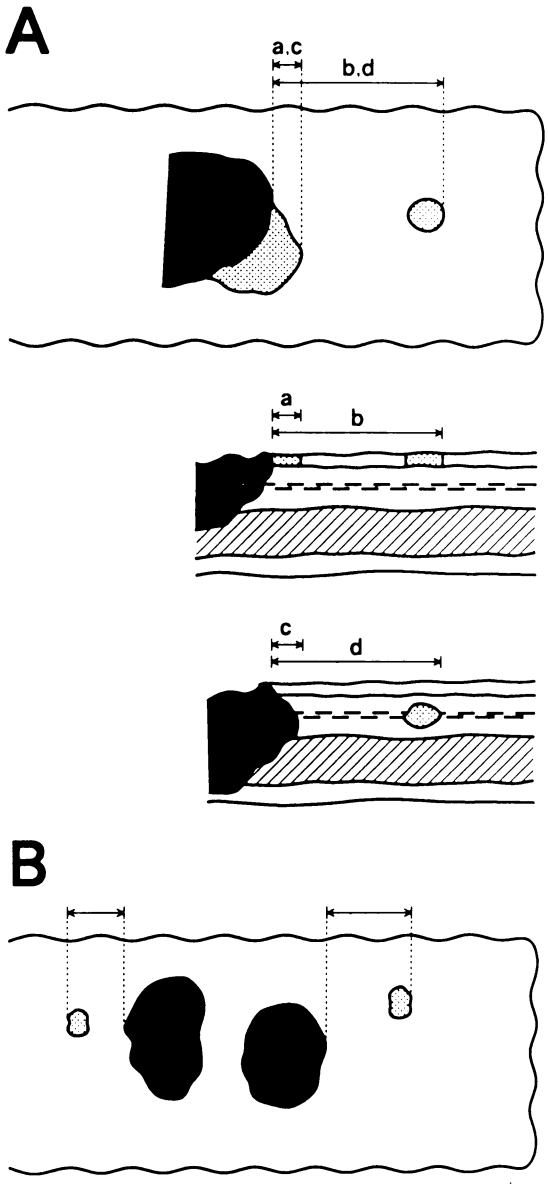

Figure 1. The method of measurement (A). The longitudinal length from the border of the main lesion to the opposite border of the accessory lesion was measured on the microscopic slide (a: contiguous IEC, b: isolated IEC, c: subepithelial direct extension and d: intramural metastasis or lymphatic or blood vessel invasion). In the specimens in which there were more than two main lesions (B), the length from the proximal border of the proximal main lesion to the proximal accessory lesion and from the distal border of the distal main lesion to the distal accessory lesion was measured.

mary esophageal carcinoma, not located within a vessel lumen but rather invading the esophageal or gastric wall and 2) the primary carcinoma and the focus of intramural metastasis distant from each other, the distance between the two lesions always ≥ 5 mm.

RESULTS

In 6 of the 420 cases, the lesions were only restricted to the epithelium and there were no lesions invading beyond the epithelium. In 95 cases, after preoperative treatment, because the main lesion was either completely destroyed or covered with a regenerative epithelium, the border of the main lesion could not be precisely identified. In 16 cases, SCC showed a widespread superficial type, in which the lesion consisted mainly of widespread intraepithelial carcinoma and various invasive parts of SCC existed in the widespread intraepithelial carcinoma (Fig. 3). Because contiguous IEC, isolated IEC, and the invasive parts of SCC coexisted intricately, it was difficult to clearly determine the border of the main lesion. Following examination was made in 303 specimens, except for these 117 specimens.

There was a single main lesion in 286 of the 303 cases, in which the main lesion was restricted to either the mucosa or submucosa in 68 cases, restricted to the muscularis propria in 29 cases, invading the adventitia in 116 cases, and invading the neighboring structures in 73 cases. There were more than two main lesions in the other 17 cases, in which a proximal and distal main lesion were restricted to either the mucosa or submucosa in 9 and 5 cases, restricted to the muscularis propria in 1 and 2 cases, invading the adventitia in 4 and 9 cases, and invading the neighboring structures in 3 and 1 cases, respectively.

The Clearance of the Resected Specimens

The average length of clearance of the proximal and distal margin in the 303 specimens was 2.8 cm (range 0–10.6 cm) and 7.1 cm (range 0.1–24.0 cm), respectively. A positive resection margin, in which there was SCC tissue within 5 mm from the resection stump, was detected in 17 (5.6%) proximal sites and 2 (0.7%) distal sites. The 19 lesions that caused positive resection margins consisted of 3 main lesions, 2 contiguous IECs, 2 isolated IECs, 3 subepithelial direct extensions, 5 intramural metastases and 4 lymphatic or blood vessel invasions.

The Incidence and Mode of Accessory Lesions

The incidence and mode of accessc lesions on the proximal and distal site, in relation to the depth of the main lesion, is shown in Table 1. There were 187 (62%) and 175 (58%) accessory lesions on the proximal and distal site, respectively, and there were no differences in mode of accessory lesions between the r oximal and distal sites at any depth of the main lesio.. There were no differences in the overall incidence of accessory lesion at any depth of the main lesion, although contiguous IEC existed in 69 (46%) of 150 sites of main lesions restricted to the mucosa or submucosa and subepithelial lesions existed in 131 (54%) of 245 sites and 82 5%) of 150 sites

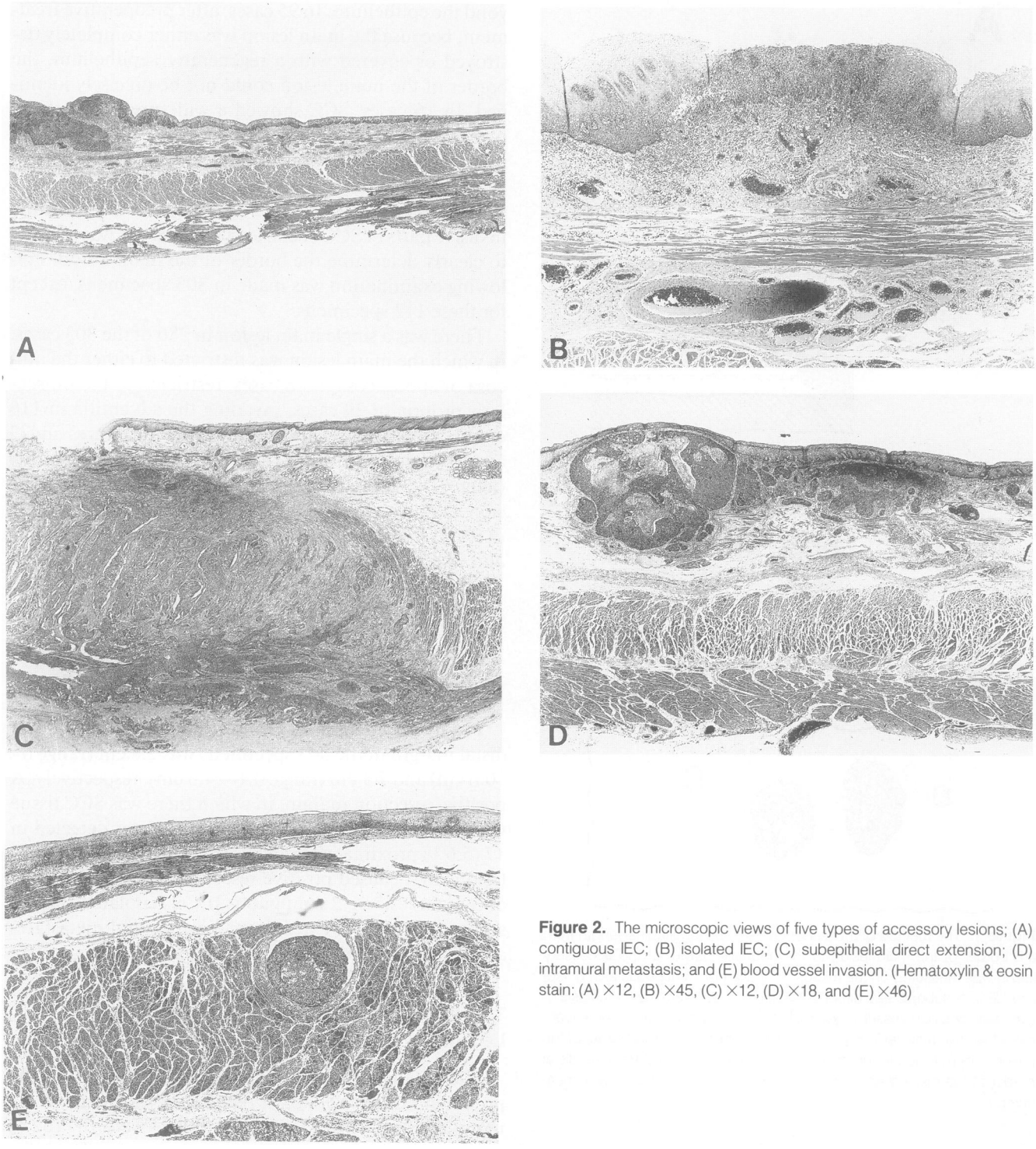

Figure 2. The microscopic views of five types of accessory lesions; (A) contiguous IEC; (B) isolated IEC; (C) subepithelial direct extension; (D) intramural metastasis; and (E) blood vessel invasion. (Hematoxylin & eosin stain: (A) ×12, (B) ×45, (C) ×12, (D) ×18, and (E) ×46)

of main lesions invading an adventitia and neighboring structures, respectively. There were no differences in the incidence of isolated IEC at any depth of the main lesion. The incidence and mode of accessory lesions in relation to the grade of differentiation of SCC is shown in Table 2. There were no differences in the incidence or mode of accessory lesions at any grade of differentiation of SCC.

The Extent of Accessory Lesions

The distribution of the extent of contiguous IEC, isolated IEC, and subepithelial accessory lesions from the border of the main lesion at the proximal and distal sites is shown in Table 3. The extent of contiguous IEC was within 30 mm from the main lesion, whereas the extent

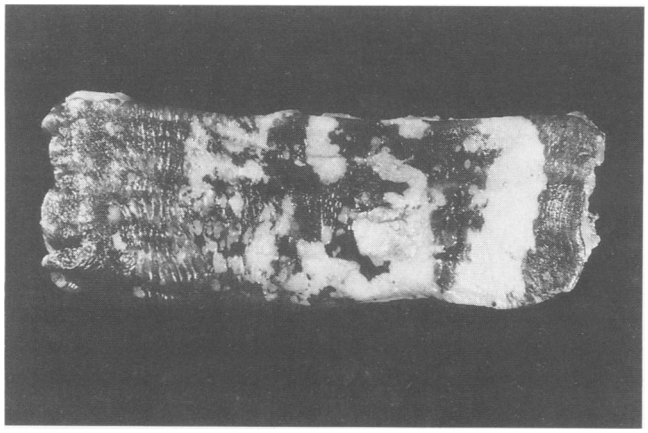

Figure 3. The macroscopic view of the widespread superficial type SCC in the esophagus. The lesion consisted of widespread intraepithelial carcinoma that was 10 cm in longitudinal length and eight invasive parts invading the mucosa or submucosa. Lugol's staining clearly demonstrated the extent of these lesions.

of isolated IEC varied greatly and the maximal extent of isolated IEC was 120 mm. There was little difference in the extent of accessory lesions between the proximal and distal sites, whereas the incidence of the lesion beyond 30 mm from the main lesion was slightly higher at the distal site than at the proximal site. Fourteen accessory lesions existed beyond 50 mm at the distal site, whereas 3 accessory lesions existed beyond 50 mm at the proximal site. The distribution of the extent of subepithelial accessory lesions is shown in Table 4. The extent of subepithelial direct extension was, except for one lesion, within 20 mm from the main lesion; the extent of intramural metastasis and lymphatic or blood vessel invasion varied greatly beyond 50 mm from the main lesion. The maximal extent of intramural metastasis and lymphatic or blood vessel invasion was 106 mm and 79 mm from the main lesion, respectively. Although 17 of 48 intramural metastases invaded the epithelium and caused either erosion or ulceration, these lesions were included into the group of subepithelial lesions.

The Risk of a Positive Resection Margin

The risk of a positive resection margin is shown in Table 5. The risk was calculated from the incidence of the accessory lesions that existed beyond the length of the clearance among the total sites of the main lesion at each depth. In other words, the risk means that the accessory lesions may remain in the remnant esophagus when the clearance of the resection margin is indicated. The risk of a positive resection margin also was calculated at 220 sites of main lesions invading the adventitia or the neighboring structures, in cases in which the operation was thought to be potentially curative. The risk of a positive resection margin due to subepithelial lesions was less than 5% at 10 mm in the main lesion restricted to either the mucosa or submucosa, 10 mm in the main lesion restricted to the muscuralis propria, and 30 mm in the main lesion invading the adventitia in the potentially curative operation cases.

DISCUSSION

In pathologic studies for rectal cancer, the extent of submucosal spread was measured and a clearance of 1.5 cm to 2.5 cm was proposed for a safe distal resection margin.[12–14] As far as the safe surgical margin for esophageal SCC is concerned, two other pathologic findings, the multiplicity of esophageal SCC and intramural vas-

Table 1. ACCESSORY LESIONS ON THE PROXIMAL AND DISTAL SITE IN RELATION TO THE DEPTH OF THE MAIN LESION

Site	Depth of the Main Lesion	Direct Margin	Accessory Lesion	Mode of Accessory Lesions		
				Contiguous IEC	Isolated IEC	Subepithelial
Proximal	Mucosa, submucosa (n = 77)	31 (40)	46 (60)	36 (47)	4 (5)	8 (10)
	Muscuralis propria (n = 30)	15 (50)	15 (50)	5 (17)	1 (3)	10 (33)
	Adventitia (n = 120)	39 (32)	81 (68)	12 (10)	8 (7)	67 (56)
	Neighboring structures (n = 76)	31 (41)	45 (59)	5 (7)	3 (4)	41 (54)
	Total (n = 303)	116 (38)	187 (62)	58 (19)	16 (5)	126 (42)
Distal	Mucosa, submucosa (n = 73)	30 (41)	43 (59)	33 (45)	6 (8)	7 (10)
	Muscuralis propria (n = 31)	15 (48)	16 (52)	6 (19)	2 (7)	11 (36)
	Adventitia (n = 125)	56 (45)	69 (55)	6 (5)	2 (2)	64 (51)
	Neighboring structures (n = 74)	27 (36)	47 (64)	7 (10)	5 (7)	41 (55)
	Total (n = 303)	128 (42)	175 (58)	52 (17)	15 (5)	123 (41)

Values in parentheses represent the percentages.

Table 2. ACCESSORY LESIONS AND THE GRADE OF SCC DIFFERENTIATION

Grade of SCC Differentiation	Depth of the Main Lesion*	Direct Margin (%)	Accessory Lesion (%)	Mode of Accessory Lesions		
				Contiguous IEC (%)	Isolated IEC (%)	Subepithelial (%)
Well	Mucosa, submucosa (n = 16)	6 (37)	10 (63)	9 (56)	1 (6)	1 (6)
	Muscularis propria (n = 7)	6 (86)	1 (14)	1 (14)	0 (0)	0 (0)
	Adventitia, Neighboring structures (n = 50)	17 (34)	33 (66)	3 (6)	1 (2)	30 (60)
Moderately	Mucosa, submucosa (n = 100)	43 (43)	57 (57)	42 (42)	5 (5)	11 (11)
	Muscularis propria (n = 35)	20 (57)	15 (43)	4 (11)	1 (3)	11 (31)
	Adventitia, Neighboring structures (n = 244)	106 (43)	138 (57)	13 (5)	9 (4)	124 (51)
Poorly	Mucosa, submucosa (n = 34)	12 (35)	22 (65)	18 (53)	4 (12)	3 (9)
	Muscularis propria (n = 19)	4 (21)	15 (79)	6 (32)	2 (11)	10 (53)
	Adventitia, Neighboring structures (n = 101)	30 (30)	71 (70)	14 (14)	8 (8)	59 (58)

IEC = intraepithelial carcinoma.

Table 3. THE EXTENT OF ACCESSORY LESIONS FROM THE BORDER OF THE MAIN LESION AT THE PROXIMAL AND DISTAL SITE

Site	Depth of the Main Lesion	Mode of Accessory Lesions	Extent from the Border of the Main Lesion (mm)							Total
			−5	−10	−20	−30	−40	−50	51−	
Proximal	Mucosa, submucosa (n = 77)	Contiguous IEC	20	9	4	3	–	–	–	36
		Isolated IEC	–	–	1	2	1	–	–	4
		Subepithelial	5	–	–	1	–	1	1	8
	Muscuralis propria (n = 30)	Contiguous IEC	1	4	–	–	–	–	–	5
		Isolated IEC	–	–	–	1	–	–	–	1
		Subepithelial	7	3	–	–	–	–	–	10
	Adventitia (n = 120)	Contiguous IEC	7	4	1	–	–	–	–	12
		Isolated IEC	2	1	–	2	2	1	–	8
		Subepithelial	26	22	10	4	3	–	2	67
	Neighboring structures (n = 76)	Contiguous IEC	3	2	–	–	–	–	–	5
		Isolated IEC	–	1	2	–	–	–	–	3
		Subepithelial	16	15	7	2	–	1	–	41
Distal	Mucosa, submucosa (n = 73)	Contiguous IEC	25	4	3	1	–	–	–	33
		Isolated IEC	–	–	1	1	1	–	3	6
		Subepithelial	1	2	1	–	2	1	–	7
	Muscuralis propria (n = 31)	Contiguous IEC	3	3	–	–	–	–	–	6
		Isolated IEC	–	–	1	–	1	–	–	2
		Subepithelial	7	2	–	1	–	–	1	11
	Adventitia (n = 125)	Contiguous IEC	3	2	1	–	–	–	–	6
		Isolated IEC	–	1	–	–	–	–	1	2
		Subepithelial	23	23	7	4	1	3	3	64
	Neighboring structures (n = 74)	Contiguous IEC	4	3	–	–	–	–	–	7
		Isolated IEC	–	2	1	–	1	–	1	5
		Subepithelial	11	10	4	3	6	2	5	41

IEC = intraepithelial carcinoma.

Table 4. THE EXTENT OF SUBEPITHELIAL ACCESSORY LESIONS FROM THE BORDER OF THE MAIN LESION

Depth of the Main Lesion	Mode of Subepithelial Accessory Lesions	Extent from the Border of the Main Lesion (mm)							Total
		−5	−10	−20	−30	−40	−50	50−	
Mucosa, submucosa (n = 150)	Direct extension	3	–	–	–	–	–	–	3
	Intramural metastasis	–	1	–	1	–	1	–	3
	Lymphatic or blood vessel invasion	2	2	1	–	2	1	1	9
Muscularis propria (n = 61)	Direct extension	10	4	–	–	–	–	–	14
	Intramural metastasis	–	1	–	–	–	–	–	1
	Lymphatic or blood vessel invasion	4	–	–	1	–	–	1	6
Adventitia (n = 245)	Direct extension	44	28	5	1	–	–	–	78
	Intramural metastasis	–	6 (2)	4 (2)	5 (2)	3 (1)	1	3 (1)	22
	Lymphatic or blood vessel invasion	5	11	8	2	1	2	2	31
Neighboring structures (n = 150)	Direct extension	25	12	4	–	–	–	–	41
	Intramural metastasis	–	7 (4)	4	4 (3)	3	–	3 (2)	21
	Lymphatic or blood vessel invasion	2	6	3	1	3	3	2	20

The values in parentheses represent number of the lesions which caused either an erosion or ulceration.

cular spread, also should be considered.[7] The multiplicity of primary esophageal SCC has been reported previously,[19] and in this study, there were more than two main lesions in 17 cases, in addition to 31 isolated IECs and 16 widespread superficial types of SCC. However, because it was not believed to be difficult to detect lesions invading beyond the epithelium in preoperative examinations, the lesions invading beyond the epithelium, even if they were multifocal, were included as the main lesions, and the attention to epithelial accessory lesion was directed only to intraepithelial carcinoma consisting of contiguous IEC and isolated IEC. On the other hand, the attention to subepithelial accessory lesion, in addition to subepithelial direct extension that was explored in the pathologic studies for rectal cancer,[13] was directed to two subepithelial accessory lesions— intramural metastasis, which means a growth in the esophageal or gastric wall after intramural vascular spread, and lymphatic or blood vessel invasion, which means an existence in the way of intramural vascular spread.

It has yet to be clarified whether there is a difference in the incidence, mode, and extent of accessory lesions

Table 5. THE RISK OF A POSITIVE RESECTION MARGIN IN RELATION TO THE LENGTH OF CLEARANCE OF THE RESECTION MARGIN

Accessory Lesion	Depth of the Main Lesion	The Length of Clearance of the Resection Margin (mm)						
		0	5	10	20	30	40	50
Epithelial	Mucosa, submucosa (n = 150)	50.7	22.0	14.0	8.0	3.3	2.0	2.0
	Muscularis propria (n = 61)	23.0	16.4	4.9	3.3	1.6	0	0
	Adventitia (n = 245)	10.6	6.1	3.3	2.4	1.6	0.8	0.4
	Neighboring structures (n = 150)	12.0	7.3	3.3	1.3	1.3	0.7	0.7
	Curative cases in adventitia + Neighboring structures (n = 220)	11.8	6.4	3.6	2.7	1.8	0.9	0.5
Subepithelial	Mucosa, submucosa (n = 150)	10.0	6.7	4.7	4.0	3.3	2.0	0.7
	Muscularis propria (n = 61)	34.4	11.5	3.3	3.3	1.6	1.6	1.6
	Adventitia (n = 245)	53.5	33.5	15.1	8.2	4.9	3.3	2.0
	Neighboring structures (n = 150)	54.7	36.7	20.0	12.7	9.3	5.3	3.3
	Curative cases in Adventitia + Neighboring structures (n = 220)	51.4	31.8	12.7	7.3	4.1	2.3	1.8

of esophageal SCC between the proximal and distal sites.[18–20] Although it is ideal to examine the resected esophagus with a long proximal clearance, as with specimens prepared by an abdominoperitoneal resection in studies on rectal cancer,[14] most of the specimens in the current study were prepared by either a subtotal or a distal partial esophagectomy and the length of the proximal clearance was shorter than that of the distal clearance. The measurements in this study were performed on the distal site and on the proximal site to examine the accessory lesions existing at distant areas from the main lesion. As a result, there were no differences in the incidence or mode of accessory lesions between the proximal and distal sites, although the incidence of accessory lesions existing beyond 5 cm from the main lesion was higher on the distal site than on the proximal site. This seems to indicate the possibility of the existence of accessory lesions in the remnant proximal esophagus rather than a difference in the extent of accessory lesions between the proximal and distal sites.

Shrinkage of the Resected Specimens

The free margins of resected specimens of the gastrointestinal tract shrink after a resection, and further shrinkage occurs when the specimen is fixed in formalin solutions. Siu et al. examined the degree of shrinkage of the resection margins of the esophagus.[21] The proximal and distal margins were reduced to 73% and 89% of their *in situ* lengths when the removed specimens had been stretched maximally, 44% and 54% with the specimens lying free, and 32% and 39% after fixation, respectively. Because the specimens in the current study usually were pinned onto a cork board when the removed specimens were stretched, the data of this pathologic study are thought to be equal to approximately three fourths of their *in situ* length.

Epithelial Accessory Lesions

We previously reported that the incidence of intraepithelial carcinoma concomitant with the main lesion was higher in early-stage SCC than in the advanced SCC of the esophagus.[20] We also reported the coexistence of glandular or mucous secreting areas and intraepithelial carcinoma concomitant with the main lesion[22,23] and the multiplicity of primary SCC of the esophagus.[19] Based on these findings, we proposed the concept of multicentric or field carcinogenesis of SCC of the esophagus. The contiguous IEC on the proximal and distal site of the main lesion also was present frequently in main lesions restricted to either the mucosa or submucosa. Futhermore, this concept was represented most peculiarly by the widespread superficial type of SCC,[24] which was recognized in 16 cases of the current study. Thus, the concept of multicentric or field carcinogenesis of esophageal SCC is considered to demonstrate the importance of intraepithelial carcinoma in determining the resection margin for early-stage esophageal SCC and the widespread superficial type of SCC.

The normal squamous epithelium includes glycogen, which interacts with the iodine of Lugol's solution, and the epithelium turns a uniform greenish-brown, whereas SCC does not include gylcogen and hence, is not stained with iodine. We reported that Lugol-combined endoscopy aids in detecting early-stage carcinoma and the spread of epithelial lesions in the esophagus[25,26]; the efficiency of Lugol-combined endoscopy also has been reported.[27–29] Furthermore, we used the Lugol's stain method to confirm the resection margin in intraoperative observation of the resected specimen and in intraoperative endoscopic examination.[30,31] These findings indicate that it is possible to detect the accurate extent of contiguous IEC in preoperative and intraoperative examinations using the Lugol's stain method, even if contiguous IEC extends 3 cm from the main lesion or even in widespread superficial type of SCC. Although two contiguous IECs caused a positive resection margin, which indicated that cancer tissue remained within 5 mm from the resection stump,[32] one clearance of the resection margin was 4 mm and an additional resection with a stapling apparatus was performed on the other case, although it was confirmed intraoperatively that no epithelial lesion remained in the remnant proximal esophagus. However, two isolated IECs caused a positive resection margin. Although one case was resected before the introduction of the Lugol's stain method, the other lesion was not detected before a pathologic examination of the resected specimen. Therefore, it is necessary for isolated IEC to be examined more carefully throughout the entire esophagus because there were no tendencies in the extent of isolated IEC at any depth of the main lesion, and isolated IEC itself usually is less than 10 mm in length.

Subepithelial Accessory Lesions

Subepithelial accessory lesions were the major cause of a positive resection margin because these lesions usually were not detected, even in intraoperative observation of the resected esophagus. Although approximately one third of intramural metastasis caused an erosion or ulceration and these intramural metastases usually could be detected preoperatively,[18] these lesions were included as subepithelial accessory lesions because they were thought to be advanced features following subepithelial lesions. The extent of subepithelial direct extension was, except for one lesion, within 20 mm from the main le-

sion, and these findings were not very different from the submucosal spread of rectal cancer.[12–14] Because satellite lesions rarely were present in rectal cancer, a clearance of 2.5 cm was acceptable for rectal cancer.[14] In esophageal SCC, however, subepithelial accessory lesions consisting of intramural metastasis and lymphatic or blood vessel invasion, often existed beyond 2 cm from the main lesion, and the extent of 12 subepithelial accessory lesions were beyond 5 cm from the main lesion. Takubo et al. reported the intramural metastasis, which existed 16.3 cm apart from the main lesion.[18] It has been reported that the two subepithelial lesions frequently were detected in the advanced esophageal SCC and the prognosis of the cases with the two subepithelial lesions were worse than that of the cases without the two subepithelial lesions.[3,18,33,34] In 7 of the 12 cases with distant intramural spread in this study, the operations were palliative because the main lesions invaded the neighboring structures or there were distant metastases at the operation. All of the other 5 patients died of distant metastases within 10 months postoperatively, although the operation was thought to be potentially curative.

A distant intramural spread of rectal cancer generally was detected in poorly differentiated adenocarcinoma[12–14]; however, there were no differences in the incidence or mode of accessory lesion in relation to the grade of differentiation of esophageal SCC, and the 12 main lesions with a distant intramural spread consisted of one well, 7 moderately, and 4 poorly differentiated SCCs.

The Risk of a Positive Resection Margin

Henessy and O'Connell reported a series of esophagectomy cases in which a clearance of 5 cm was attempted and described that the proximal resection margin was microscopically involved in 11 (15%) of 72 cases and that eight (14%) anastomotic recurrences causing recurrent dysphagia occurred among the 56 survivors.[4] Tam et al. reported the incidence of local recurrence in relation to the proximal resection margin.[5] In the 100 cases consisting of curative and palliative cases, 4 (20%) of 20 cases had an anastomotic recurrence when the *in situ* resection margin was less than 5 cm, and 4 (8%) of 49 cases had an anastomotic recurrence when the margin was between 5 and 10 cm. These findings are consistent with the pathologic data of the current study. Tam et al. also reported that none of the 25 cases had a recurrence when the *in situ* resection margin was greater than 10 cm and that none of the 14 cases in which the depth of the tumors were restricted within the muscularis propria had recurrences.[5] Our pathologic data, however, suggested the possibility of a positive resection margin, even in these cases.

The existence of a distant intramural spread indicates that a resection of the entire esophagus is needed if it is hoped that the risk of a positive resection margin is null. However, most patients with rectal cancer with distant intramural spread died of distant metastases, not of local recurrences.[14] Concerning patients with a distant intramural spread of the esophageal cancer, Akiyama described that the resection margin is not a realistic proposition and may not even be in the patient's best interest.[7] How long, then, is an adequate safe resection margin? Although intramural metastasis and lymphatic or blood vessel invasion are without a doubt related to intramural vascular spread, the existence of the two subepithelial accessory lesions does not necessarily indicate distant metastasis. The fact that the decrease of the risk of a positive resection margin was not greater, even if the length of the clearance was longer when the risk of a positive resection margin was below 5%, offers the key for determining the clearance of a safe resection margin. The risk of a positive resection margin due to subepithelial accessory lesions was less than 5% at 10 mm in the main lesion, restricted to the submucosa or the muscularis propria, and at 30 mm in the main lesion, invading the adventitia in the potentially curative operation cases. We believe that such a clearance is acceptable if it is noted that subepithelial accessory lesions may remain beyond the clearance at an incidence of 5%, even in the main lesion restricted to the submucosa or in the potentially curative cases. On the other hand, a clearance of the resection margin for palliative operation may be less than such a clearance, if it is permissible that the risk of a positive resection margin would increase.

Summary

We believe that 1) contiguous IEC frequently existed in early-stage esophageal SCC and subepithelial accessory lesions frequently existed in advanced esophageal SCC; 2) the extent of contiguous IEC and isolated IEC should be accurately determined using the Lugol's stain method, especially in cases of early-stage esophageal SCC or widespread superficial types of SCC; 3) a clearance of the resection margin of 10 mm and 30 mm is acceptable for the main lesion restricted to the submucosa or muscularis propria and for the main lesion invading an adventitia in the potentially curative operation cases, respectively, although the shrinkage of the resected specimens should be considered in determining the *in situ* resection margin; and 4) if these clearances of the resection margin are accepted, however, it should be noted that subepithelial accessory lesions may remain beyond the clearance at an incidence of 5%, even in submucosal cancer or potentially curative cases.

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